Recommendations for the Use of Antiretroviral Drugs in Pregnant Women with HIV Infection and Interventions to Reduce Perinatal HIV Transmission in the United States

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Teratogenicity (Last updated December 12, 2019; last reviewed December 12, 2019)

Panel's Recommendations

- All cases of antiretroviral (ARV) drug exposure during pregnancy should be reported to the Antiretroviral Pregnancy Registry **(AIII)**.
- Based on multiple studies indicating no difference in rates of total birth defects for first-trimester exposure compared with later ARV drug exposures, women can be counseled that ARV drugs during pregnancy generally do not increase the risk of birth defects **(BIII)**; a possible exception is a small increased risk of neural tube defects (NTDs) with dolutegravir (DTG) use during the periconception period. Providers should be aware that data on the risks of birth defects for many ARV drugs are limited.

Updated Panel Recommendations Regarding the Use of Dolutegravir at the Time of Conception and During Pregnancy:

- DTG exposure around the time of conception has been associated with a small but significant increase in the risk of infant NTDs in Botswana (0.3%), where food is not routinely fortified with folate. Although this risk was higher than the risk for NTDs in infants born to women who were receiving efavirenz (0.05%) and women without HIV (0.08%), there are not enough data to determine the risk of NTDs with preconception use of all *Preferred* and *Alternative* regimens, including DTG, in the United States. Based on the available evidence, the Panel on Treatment of Pregnant Women with HIV Infection and Prevention of Perinatal Transmission (the Panel) recommends DTG as a ***Preferred* drug for pregnant women, irrespective of trimester (AII)**, and an ***Alternative* drug for women who are trying to conceive (AIII)**.
- The Panel emphasizes the importance of counseling and informed decision-making regarding all ARV regimens for people with HIV **(AIII)**. For additional information, see Appendix D: Dolutegravir Counseling Guide for Health Care Providers.
- Clinicians should discuss future reproductive plans and timing as well as the risks and benefits of conceiving on specific ARV medications and use of appropriate contraceptive options to prevent unintended pregnancy **(AIII)**.
- Folic acid is known to prevent NTDs in the general population. All pregnant women and women who might conceive should take at least 400 mcg of folic acid daily **(AI)**. There is no established link between the use of DTG and impaired folate metabolism, nor is there evidence that folate supplementation prevents DTG-associated NTDs.
- For additional information, see Updated Guidance about the Use of Dolutegravir in Pregnancy in Recommendations for Use of Antiretroviral Drugs During Pregnancy, Preconception Counseling and Care for Women of Childbearing Age Living with HIV, Pregnant Women Living with HIV Who Are Currently Receiving Antiretroviral Therapy, and Dolutegravir.

Rating of Recommendations: *A = Strong; B = Moderate; C = Optional*

Rating of Evidence: *I = One or more randomized trials with clinical outcomes and/or validated laboratory endpoints; II = One or more well-designed, nonrandomized trials or observational cohort studies with long-term clinical outcomes; III = Expert opinion*

Antiretroviral Pregnancy Registry Reporting

Health care providers who are caring for pregnant women with HIV and their newborns are strongly advised to report instances of prenatal exposure to antiretroviral (ARV) drugs (either single-drug exposure or exposure to a combination of ARV drugs) to the Antiretroviral Pregnancy Registry as early in pregnancy as possible. This registry is an epidemiologic project to collect observational, nonexperimental data regarding ARV drug exposure during pregnancy for the purpose of assessing the potential teratogenicity of these drugs. Registry data will be used to supplement animal toxicology studies and assist clinicians in weighing the potential risks and benefits of treatment for individual patients. The Antiretroviral Pregnancy Registry is a collaborative project of pharmaceutical manufacturers with an advisory committee that includes a teratologist, an infectious disease specialist, an epidemiologist, a biostatistician, and a group of obstetric, maternal-fetal medicine, and pediatric providers. The registry does not use patient names, and registry staff obtain birth outcome follow-up information from the reporting health care provider.

Referrals should be directed to:

Antiretroviral Pregnancy Registry
Research Park
1011 Ashes Drive
Wilmington, NC 28405
Telephone: 1-800-258-4263
Fax: 1-800-800-1052
http://www.APRegistry.com

Antiretroviral Drugs and Birth Defects

The potential harm to the fetus from maternal ingestion of a specific drug depends not only on the drug itself, but also on the dose ingested, the gestational age of the fetus at exposure, the duration of exposure, interactions with other agents to which the fetus is exposed, and, to an unknown extent, the genetic makeup of the mother and fetus.

Information regarding the safety of using certain drugs during pregnancy is derived from animal toxicity data, anecdotal experience, registry data, and clinical trials. Drug choice should be individualized and discussed with the woman before treatment begins. Clinicians must also consider available data from preclinical and clinical testing of the individual drugs. Preclinical data include results of in vitro and animal *in vivo* screening tests for carcinogenicity, clastogenicity/mutagenicity, and reproductive and teratogenic effects. However, the predictive value of such tests for adverse effects in humans is unknown.

Data continue to be collected on the placental passage, pharmacokinetics, and safety of Food and Drug Administration (FDA)-approved ARV drugs during pregnancy, in addition to data on the long-term safety in infants who were exposed to these drugs. However, the data remains somewhat limited, especially for newer drugs (see Supplement: Safety and Toxicity of Individual Antiretroviral Agents in Pregnancy). When analyzing registry data, data on birth outcomes from 200 infants who were exposed to an ARV drug during the first trimester is viewed as sufficient to detect a 2.2-fold increase in the risk of overall birth defects associated with that drug compared to the general population. A cohort of 1,000 is sufficient to detect a 1.5-fold increase in the risk of birth defects. The general U.S. population birth defect prevalence is 2.8%.[1] However, data from a larger number of infants is required to detect an increased risk of specific birth defects with lower frequencies of occurrence, with the required number of infants who were exposed to an ARV drug increasing as the frequency of the defect in an unexposed population decreases.[2]

A recent report from the Surveillance Monitoring for ART Toxicities (SMARTT) study of the Pediatric HIV/AIDS Cohort Study (PHACS) network detected an increased rate of microcephaly in HIV-exposed but uninfected children with *in utero* efavirenz (EFV) exposure. The relative risk of microcephaly in infants with *in utero* EFV exposure was 2.56 (95% confidence interval [CI], 1.22–5.37). In this study, microcephaly was defined as a z-score of less than -2 between 6 and 36 months of age or head size below the second percentile after 36 months.[3] Only 4.7% of children had been exposed to EFV *in utero*. The relative risk of microcephaly was higher among children who had been exposed to EFV plus zidovudine (ZDV) and lamivudine (3TC) than among those who had been exposed to EFV plus tenofovir disoproxil fumarate (TDF) and emtricitabine (FTC). Children with microcephaly had lower scores on neurodevelopmental assessments at ages 1 year and 5 years and a higher rate of neurodevelopmental impairment than those without microcephaly. Additional evaluation of the association between microcephaly and *in utero* EFV exposure is needed.

It is important to consider potential confounding factors in studies of ARV drugs and birth defects. Several factors that are associated with HIV may also increase the risk of birth defects, such as exposure to folate antagonists (e.g., trimethoprim-sulfamethoxazole),[4] nutritional and folate status,[5] and tobacco and alcohol use.[6] Clinicians should also be aware of indication bias, which can occur when a patient's reason for taking a particular ARV drug is associated with an increased risk of birth defects, such as older age or more advanced disease.

Several studies of birth defects in fetuses and infants of women who received ARV regimens during observational studies found no difference in rates of total birth defects between first-trimester drug exposures and later exposures.[7-11] The Antiretroviral Pregnancy Registry conducts a primary analysis of prospective cases of ARV drug exposure during pregnancy provided by health care providers. In this analysis, the prevalence of birth defects was 2.8 per 100 live births among women with a first-trimester exposure to any ARV drug (271 of 9,854 exposures; 95% CI, 2.4–3.1). The prevalence of defects is not significantly different from that seen in women with an initial exposure during the second and/or third trimester (2.8 per 100 live births; prevalence ratio 0.99, 95% CI, 0.83–1.18).[1] Though these studies are reassuring, an increased risk of specific abnormalities, particularly rare abnormalities, would not necessarily be detectable when looking only

at the total number of birth defects. Further, risk may be underestimated when defects are only ascertained after live births, as this does not include more severe defects that result in stillbirths and terminations. Another limitation is that an increased risk that is associated with a specific ARV drug may be obscured when the analysis unit combines all ARV drugs together.

Use of Dolutegravir at the Time of Conception and in Early Pregnancy

In May 2018, an unplanned interim evaluation of a National Institutes of Health-funded, observational surveillance study of birth outcomes among pregnant women on antiretroviral therapy (ART) in Botswana revealed four neural tube defects (NTDs) among infants born to 426 women (0.94%) who became pregnant while receiving a dolutegravir (DTG)-based regimen.[12] These data were updated in a planned analysis in May 2019. In the Tsepamo study, five NTDs were identified (0.30%) among 1,683 deliveries to women who were taking DTG around the time of conception; the defects included two instances of myelomeningocele, one of anencephaly, one of encephalocele, and one of iniencephaly. In comparison, 15 NTDs were found among 14,792 deliveries (0.10%) in which the mother was taking any ART that did not include DTG at conception, three NTDs were found among 7,959 deliveries (0.04%) in which the mother was taking EFV at conception, one NTD was found among 3,840 deliveries (0.03%) in which the mother started treatment with DTG during pregnancy, and 70 NTDs were found among 89,372 deliveries (0.08%) to mothers without HIV.[13] While the risk of NTDs in infants who were exposed to DTG around the time of conception was lower than initially reported, it remains significantly increased compared to all comparison groups.

Although there are limited data on the association between NTDs and DTG exposure, three studies that included an internal comparator group and assessments of NTDs in stillbirths and terminations have evaluated NTDs in infants who were exposed to DTG at conception in addition to the Botswana study. The first was a prospective study by the Ministry of Health and the Centers for Disease Control and Prevention at 22 additional sites in Botswana that were not included in the Tsepamo study. This study identified one NTD among infants born to 152 women (0.66%) who were receiving DTG at conception, compared to no NTDs among infants born to 381 women who were receiving other ARV drugs at conception and two NTDs among infants born to 2,328 women who did not have HIV (0.09%).[14] The second study included prospective data from the Antiretroviral Pregnancy Registry, and it is worth noting that 75% of the data in the registry comes from North America, Europe, and Latin America, where most countries require folate fortification for food. The study found one case of an NTD among 248 live births (0.4%) of infants with periconception DTG exposure and no NTDs among 217 live births of infants with periconception elvitegravir (EVG) exposure and 268 live births of infants with periconception raltegravir (RAL) exposure.[1] The third study was a retrospective study of women with periconception ARV drug exposure in a national cohort in Brazil; no NTDs were observed among 384 pregnancies in which infants were exposed to DTG (95% CI, 0–0.0099) or among 1,109 pregnancies in which infants were exposed to EFV or RAL (95% CI, 0–0.003).[15] Unlike Brazil and the United States, Botswana does not have mandated food folate fortification, which can decrease NTD prevalence by half. More data are needed to delineate the risks of NTDs among infants born to women living in other geographical regions and countries with mandated food folate fortification.

No mechanism has been identified to explain the observed association between DTG exposure and NTDs, though several studies have evaluated the role of folate. A substudy of the ADVANCE trial evaluated serum folate levels among women by randomized arm and found that folate deficiency occurred less often in women who were receiving DTG, with 13.7% of women in the DTG plus TDF plus FTC arm and 5.4% of women in the DTG plus tenofovir alafenamide (TAF) plus FTC arm experiencing folate deficiency compared with 30% of those who received EFV ($P < 0.001$).[16] Studies that have evaluated folate receptor antagonism by DTG in animal models and cell models have had conflicting results, and the clinical implications of these results is unclear. Additional studies are needed to clarify the role of folate and to explore other potential mechanisms.

The risk of NTDs decreases after early pregnancy, though it is not clear exactly when this period of increased risk ends. Most NTDs result from failure of neural tube closure. The neural tube closes by

approximately 4 weeks post-conception, or approximately 6 weeks after the last menstrual period in women with regular menses. Therefore, the risk period for a medication to cause NTDs is over by approximately 6 weeks gestational age. However, it is possible that one of the five defects observed in the Botswana study (encephalocele) may have occurred by a different mechanism (a post-neurulation event) slightly after the neural tube had closed. The exact timing of development of encephalocele in humans is not well described; however, extrapolating from animal data, it is likely to occur before 6 weeks post-conception (8 weeks gestational age). Determining when the risk period for defects is over also depends on accurately determining the gestational age and the date of the last menstrual period.

Data on Other Integrase Strand Transfer Inhibitors

Limited data are available on the association between other integrase strand transfer inhibitors and birth defects. A retrospective case series evaluated data from nine institutions on 140 pregnancies in which the woman received EVG during pregnancy, including 82 women who received the drug before conception and during the first trimester.[17] Two defects were noted: one case of hydronephrosis in which exposure began before conception, and one case of an encephalocele in which a woman with periconceptional exposure to TDF plus FTC plus darunavir/ritonavir was switched to atazanavir (ATV) plus EVG/cobicistat/FTC/TDF at 9 weeks due to drug side effects. Among 33 women who were exposed to EVG during the first trimester in the United Kingdom and Ireland, no defects were noted in 31 liveborn infants.[18] In the Antiretroviral Pregnancy Registry, defects were reported in six of 240 infants (2.5%; 95% CI, 0.9% to 5.4%) born after first-trimester exposure to EVG; this does not represent an increased risk compared to the overall rate of defects in the Registry.[1] A review of the Gilead safety database, which included an earlier data set from the Antiretroviral Pregnancy Registry, reported 155 prospective periconception exposures to EVG with no NTDs.[19] Review of a surveillance database in Canada found no NTDs among 28 infants with first-trimester exposures.[11]

Surveillance data from the United Kingdom and Ireland included 882 live births of infants with exposure to RAL, and birth defects were reported in 23 infants, a rate of 2.59% (95% CI, 1.65% to 3.86%); this rate is similar to that in the general population. No NTDs were reported.[18] Among the 222 infants with periconception exposure to RAL, five defects were noted, including two heart defects, two limb defects, and one unspecified defect. In the Antiretroviral Pregnancy Registry, birth defects were reported in nine of 327 infants (2.8%; 95% CI, 1.3% to 5.2%) with first-trimester exposure to RAL. This incidence is similar to the incidence seen in the overall population reported to the APR. A review performed by Merck researchers that included data from the company database; the previously noted Antiretroviral Pregnancy Registry data; and the United Kingdom, Ireland and French pregnancy cohorts reported 456 periconception exposures to RAL with no NTDs.[20]

The Panel on Treatment of Pregnant Women with HIV Infection and Prevention of Perinatal Transmission has updated its recommendations regarding the use of DTG during pregnancy and at the time of conception in coordination with the Panel on Antiretroviral Guidelines for Adults and Adolescents (see Recommendations for Use of Antiretroviral Drugs During Pregnancy, Preconception Counseling and Care for Women of Childbearing Age Living with HIV, and the Adult and Adolescent Antiretroviral Guidelines). The potential risk of NTDs, the benefits of DTG-containing regimens, and the risks and benefits of alternative regimens should be discussed with women who need to initiate ART during the first trimester or who are planning to become pregnant (see Appendix D: Dolutegravir Counseling Guide for Health Care Providers). For additional guidance, please contact the National Perinatal HIV Hotline (1-888-448-8765).

Specific Drugs

Efavirenz

EFV use during pregnancy has received increased scrutiny because of the results of a small study in nonhuman primates. Significant malformations were observed in three of 20 infant cynomolgus monkeys that received EFV from gestational days 20 to 150 at a dose that produced plasma concentrations comparable to those seen in humans with systemic exposure to the therapeutic dose.[21] The malformations included

anencephaly and unilateral anophthalmia in one monkey, microphthalmia in another, and cleft palate in the third.

Increased scrutiny of outcomes after EFV exposure has provided reassuring data. Sufficient numbers of first-trimester exposures to EFV have been monitored in the Antiretroviral Pregnancy Registry to rule out at least a 1.5-fold increase in the risk of overall birth defects and a two-fold increase in risk of birth defects in the cardiovascular and genitourinary systems. Twenty-five of 1,061 infants (2.4%) with first-trimester exposures to EFV were found to have birth defects, including a single case of myelomeningocele and one case of anophthalmia and amniotic bands.[1] A meta-analysis that included data from 23 studies reporting on 2,026 first-trimester exposures to ARV drugs found no increased risk of overall birth defects for infants born to women who were on EFV during the first trimester compared with those who were on other ARV drugs during the first trimester (relative risk [RR] 0.78; 95% CI, 0.56–1.08). One NTD was observed, giving an incidence of 0.05% (95% CI, <0.01 to 0.28).[22] The number of reported first-trimester EFV exposures in this meta-analysis is sufficient to rule out a two-fold increase in low-incidence birth defects, such as NTDs. Incidence of NTDs in the general U.S. population is 0.02% to 0.2%.[2,22]

The Tsepamo study discussed above found three NTDs among 7,959 live births and stillbirths (0.04%) to women who were on EFV at conception. There is no difference between this incidence and the incidence for NTDs among infants born to women without HIV.[13] The study also found no increased risk of total major abnormalities identified on infant surface exam among women who were taking EFV around the time of conception compared to women without HIV (0.68% vs. 0.59%). In addition, a birth defect surveillance program in Uganda that used methods that were similar to those used in the Tsepamo study reported an NTD prevalence of 0.059% (95% CI, 0.001% to 0.118%) among infants born to women with HIV, 80% of whom were on EFV, and an NTD prevalence of 0.092% (95% CI, 0.068% to 0.116%) among infants born to women without HIV.[23] Thus, the findings in monkeys have not been confirmed by human data, underscoring the need for well-designed studies to rapidly provide data on the safety of new drugs for use in pregnancy.

The FDA advises women to avoid becoming pregnant while taking EFV and advises health care providers to avoid administering EFV during the first trimester of pregnancy, as fetal harm may occur. However, with the data from Botswana on over 7,900 periconception exposures, we can now rule out a three-fold or more increase in the risk of NTDs in infants who were exposed to EFV. As a result, the Perinatal Guidelines do not restrict the use of EFV in pregnancy or in women who are planning to become pregnant; this is consistent with the British HIV Association and World Health Organization guidelines for use of ARV drugs in pregnancy, both of which note that EFV can be used throughout pregnancy.[24,25] Importantly, women who become pregnant on EFV-containing regimens that are suppressive and tolerated should continue using those regimens.

Tenofovir Disoproxil Fumarate

TDF has not demonstrated teratogenicity in rodents or monkeys. Data from the Antiretroviral Pregnancy Registry showed that 91 of 3,851 infants born to women with first-trimester TDF exposure had birth defects. That means the birth defect incidence for infants exposed to TDF during the first trimester is 2.4%, similar to the incidence in the general population.[1] A more recent meta-analysis of TDF use among women with HIV found no increase in the risk of congenital anomalies associated with the use of TDF (RR 1.03; 95% CI, 0.83–1.28).[26]

No clinical studies have reported newborn outcomes associated with maternal use of TAF.

Zidovudine

In a study from France that included 13,124 live births that occurred between 1994 and 2010, first-trimester ARV drug exposure was found in 5,388 infants (42%). The authors reported a significant adjusted association between first-trimester ZDV exposure and congenital heart defects, primarily ventricular (58%) and atrial (18%) septal defects (adjusted odds ratio [aOR] 2.2; 95% CI, 1.3–3.7). Because fetal ultrasounds were conducted on all infants who were exposed to HIV, and because spontaneous closure of ventricular septal

defects after birth is common, the clinical significance of the cardiac findings is uncertain.[27] An analysis of 16,304 prospectively reported pregnancies compared the risk of ventricular septal defects and congenital heart defects in infants with prenatal exposure to ZDV-containing regimens and infants with prenatal exposure to ART regimens that did not contain ZDV. In contrast to the French study, this analysis found that the risk of these defects was similar between the two groups.[28] A recent study that combined a meta-analysis and data from a Medicaid database of ART prescriptions and infant outcomes did not detect a significant increase in overall defects or heart defects among infants who had first-trimester ZDV exposure compared to infants with exposure to other ART regimens during the first trimester (odds ratio [OR] for overall defects 1.11; 95% CI, 0.80–1.55; OR for cardiac defects 1.30; 95% CI, 0.63–2.71).[29] Additionally, one study investigated echocardiographic parameters of left ventricular function and structure in 417 infants. Some of the infants had been exposed to HIV and ARV drugs but had not contracted HIV, while others had not been exposed to either HIV or ARV drugs. When these children were tested at ages 2 to 7 years, no clinically significant differences in left ventricular function and structure were found between the exposed and unexposed groups.[6]

Atazanavir

In an analysis from the Pediatric HIV/AIDS Cohort Study that included 2,580 live births, first-trimester ARV drug exposure overall was not associated with an increased risk of birth defects.[30] First-trimester exposures to ATV were reported for 222 infants, and in adjusted analyses, ATV was the only individual ARV drug for which first-trimester exposure was associated with birth defects (primarily skin and musculoskeletal defects). However, in the Antiretroviral Pregnancy Registry, there was no increase in the risk of birth defects with first-trimester ATV exposure among 1,328 births.[1]

Other Antiretroviral Drugs

In the Antiretroviral Pregnancy Registry, sufficient numbers of first-trimester exposures have been monitored to detect at least a two-fold increase in the risk of overall birth defects for cobicistat, darunavir, didanosine (ddI), EVG, indinavir, RAL, rilpivirine, stavudine, and telbivudine; however, no such increases have been detected to date. For abacavir, ATV, EFV, FTC, 3TC, lopinavir, nelfinavir (NFV), nevirapine, ritonavir, TDF, and ZDV, sufficient numbers of first-trimester exposures have been monitored to detect at least a 1.5-fold increase in the risk of overall birth defects and a two-fold increase in the risk of birth defects in cardiovascular and genitourinary systems; no such increases have been detected to date. A modest (but statistically significant) increase in overall birth defect rates for ddI and NFV is observed when data from the Antiretroviral Pregnancy Registry are compared with the U.S. population-based Metropolitan Atlanta Congenital Defects Program (MACDP) surveillance data.[1] The lower bounds of the CIs for ddI and NFV (2.9% and 2.8%, respectively) are slightly above the higher bound (2.72%) for the MACDP rate, but rates are not elevated compared to the Texas Birth Defect Registry rate of 4.17%, an additional comparator now included in the Antiretroviral Pregnancy Registry. No specific pattern of defects has been detected with the use of either ddI or NFV, and the clinical relevance of this statistical finding is unclear. The Antiretroviral Pregnancy Registry will continue to monitor ddI and NFV for any signal or pattern of birth defects.

See Supplement: Safety and Toxicity of Individual Antiretroviral Agents in Pregnancy for detailed information on individual drugs.

References

1. Antiretroviral Pregnancy Registry Steering Committee. Antiretroviral Pregnancy Registry international interim report for 1 January 1989–31 January 2019. Wilmington, NC: Registry Coordinating Center. 2019. Available at: http://www.apregistry.com.

2. Watts DH. Teratogenicity risk of antiretroviral therapy in pregnancy. *Curr HIV/AIDS Rep*. 2007;4(3):135-140. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17883999.

3. Williams PL, Yildirim C, Chadwick EG, et al. Association of maternal antiretroviral use with microcephaly in children

who are HIV-exposed but uninfected (SMARTT): a prospective cohort study. *Lancet HIV*. 2019;S2352-3018(19)30340-6. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31740351.

4. Ford N, Shubber Z, Jao J, Abrams EJ, Frigati L, Mofenson L. Safety of cotrimoxazole in pregnancy: a systematic review and meta-analysis. *J Acquir Immune Defic Syndr*. 2014;66(5):512-521. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24853309.

5. Jungmann EM, Mercey D, DeRuiter A, et al. Is first trimester exposure to the combination of antiretroviral therapy and folate antagonists a risk factor for congenital abnormalities? *Sex Transm Infect*. 2001;77(6):441-443. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11714944.

6. Lipshultz SE, Williams PL, Zeldow B, et al. Cardiac effects of in-utero exposure to antiretroviral therapy in HIV-uninfected children born to HIV-infected mothers. *AIDS*. 2015;29(1):91-100. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25562493.

7. Watts DH, Huang S, Culnane M, et al. Birth defects among a cohort of infants born to HIV-infected women on antiretroviral medication. *J Perinat Med*. 2011;39(2):163-170. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21142844.

8. Knapp KM, Brogly SB, Muenz DG, et al. Prevalence of congenital anomalies in infants with *in utero* exposure to antiretrovirals. *Pediatr Infect Dis J*. 2012;31(2):164-170. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21983213.

9. da Costa TP, Machado ES, et al. Malformations among HIV vertically exposed newborns–results from a Brazilian cohort study. Presented at: 6th IAS Conference on HIV Pathogenesis and Treatment and Prevention. 2011. Rome, Italy.

10. Floridia M, Mastroiacovo P, Tamburrini E, et al. Birth defects in a national cohort of pregnant women with HIV infection in Italy, 2001-2011. *BJOG*. 2013;120(12):1466-1475. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23721372.

11. Money D, Lee T, O'Brien C, et al. Congenital anomalies following antenatal exposure to dolutegravir: a Canadian surveillance study. *BJOG*. 2019;126(11):1338-1345. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31188522.

12. Zash R, Makhema J, Shapiro RL. Neural-tube defects with dolutegravir treatment from the time of conception. *N Engl J Med*. 2018;379(10):979-981 Available at: https://www.ncbi.nlm.nih.gov/pubmed/30037297.

13. Zash R, Holmes L, Diseko M, et al. Neural-tube defects and antiretroviral treatment regimens in Botswana. *N Engl J Med*. 2019;381(9):827-840. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31329379.

14. Raesima M, Forhan S, Thomas V, Rabold E, et al. Addressing the safety signal with dolutegravir use at conception: Additional surveillance data from Botswana. Presented at: International AIDS Society Conference. 2019. Mexico City, Mexico.

15. Pereira G, Kim A, Jalil E, Fernandes F, Shepard B, Veloso V, et al. No occurrences of neural tube defects among 382 women on dolutegravir at pregnancy conception in Brazil. Presented at: International AIDS Society Conference. 2019. Mexico City, Mexico.

16. Chandiwana N, Hill A, Chersich M, et al. Serum folate and birth outcomes: DTG vs. EFV trial evidence in South Africa. Presented at: Conference on Retroviruses and Opportunistic Infections. 2019. Seattle, Washington.

17. Badell ML, Sheth AN, Momplaisir F, et al. A multicenter analysis of elvitegravir use during pregnancy on HIV viral suppression and perinatal outcomes. *Open Forum Infect Dis*. 2019;6(4):ofz129. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31037241.

18. Rasi V, Cortina-Borja M, Peters H, Sconza R, Thorne C. Brief report: surveillance of congenital anomalies after exposure to raltegravir or elvitegravir during pregnancy in the United Kingdom and Ireland, 2008-2018. *J Acquir Immune Defic Syndr*. 2019;80(3):264-268. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30531300.

19. Farrow T, Deaton C, Nguyen N, Serejo M, Muramoto D, etc. Cumulative safety review of elvitegravir and bictegravir use during pregnancy and risk of neural tube defects. Abstract P030. Presented at: HIV Drug Therapy. 2018. Glasgow, United Kingdom. Available at: http://hivglasgow.org/wp-content/uploads/2018/11/P030-4.pdf.

20. Shamsuddin H, Raudenbush CL, Sciba BL, et al. Evaluation of neural tube defects (NTDs) after exposure to raltegravir during pregnancy. *J Acquir Immune Defic Syndr*. 2019;81(3):247-250. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30908331.

21. Efavirenz [package insert]. Food and Drug Administration. 2019. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/020972s057,021360s045lbl.pdf.

22. Ford N, Mofenson L, Shubber Z, et al. Safety of efavirenz in the first trimester of pregnancy: an updated systematic review and meta-analysis. *AIDS*. 2014;28 Suppl 2:S123-131. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24849471.

23. Barlow-Mosha L, Mumpe D, Williamson D, et al. Neural tube defects, HIV, and antiretrovirals: birth-defect surveillance in Uganda. Presented at: Conference on Retroviruses and Opportunistic Infections. 2019. Seattle, Washington.

24. de Ruiter A, Taylor GP, Clayden P, et al. British HIV Association guidelines for the management of HIV infection in pregnant women 2012 (2014 interim review). *HIV Med*. 2014;15 Suppl 4:1-77. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25604045.

25. British HIV Association. British HIV association guidelines for the management of HIV in pregnancy and postpartum 2018. *HIV Med*. 2019;20 Suppl 3:s2-s85. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30869192.

26. Nachega JB, Uthman OA, Mofenson LM, et al. Safety of tenofovir disoproxil fumarate-based antiretroviral therapy regimens in pregnancy for HIV-infected women and their Infants: a systematic review and meta-analysis. *J Acquir Immune Defic Syndr*. 2017;76(1):1-12. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28291053.

27. Mofenson LM, Watts DH. Safety of pediatric HIV elimination: the growing population of HIV- and antiretroviral-exposed but uninfected infants. *PLoS Med*. 2014;11(4):e1001636. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24781352.

28. Vannappagari V, Albano JD, Koram N, Tilson H, Scheuerle AE, Napier MD. Prenatal exposure to zidovudine and risk for ventricular septal defects and congenital heart defects: data from the antiretroviral pregnancy registry. *Eur J Obstet Gynecol Reprod Biol*. 2016;197:6-10. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26687320.

29. Rough K, Sun JW, Seage GR, 3rd, et al. Zidovudine use in pregnancy and congenital malformations. *AIDS*. 2017;31(12):1733-1743. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28537936.

30. Williams PL, Crain MJ, Yildirim C, et al. Congenital anomalies and *in utero* antiretroviral exposure in human immunodeficiency virus-exposed uninfected infants. *JAMA Pediatr*. 2015;169(1):48-55. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25383770.